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Toxicology data in the service of hazard identification:

FRAMEWORK FOR EVALUATING A POSTULATED CARCINOGENIC MODE OF ACTION

'Mode of action' is contrasted with 'mechanisms of action', which implies a more detailed, molecular description of key processes and events than is meant by mode of action.

Examples of mode of action: mutagenicity, mitogenesis, inhibition of apoptosis, cytotoxicity with reparative cell proliferation, immune suppression

Data to be reviewed in analyzing mode of action, with overall weighing of evidence laying out strengths, weaknesses and uncertainties of the case in question, as well as potential alternative positions and rationalities. Identifying data gaps and research needs is part of the assessment

Description of the postulated mechanism of action, e.g., thyroid disruption

Topics:

Identify key event

- can a list of events be identified that are key to the carcinogenic process?
- Are the vents well defined?

Dose-response analysis

- what are the correlations among doses producing events and cancer?

Temporal relationship

- What is the ordering of events that underlie the carcinogenic process?

Strength, consistency, specificity of association

- What is the level of statistical and biological significance for each event and for cancer?
- Do independent studies produce the same associations?
- Does the agent produce effects other than postulated?
- Is the key event associated with precursor lesions?

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Source: https://www.industrydocuments.ucsf.edu/docs/fpgj0001

Biological plausibility and coherence

- Is the mode of action consistent with what is known about carcinogenesis in general and for the case specifically?
- Are carcinogenic effects and events consistent across structural analogs?
- Is the database on the agent internally consistent in supporting the purported mode of action, including relevant noncancer toxicities?

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